Chapter 6
Solid Dispersions based on inulin for the stabilization and formulation of Δ^9-tetrahydrocannabinol

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Published in Eur. J. of Pharm. Sci. 2004, 21(4), 511-518

Keywords: Δ^9-THC, lyophilization, tertiary butyl alcohol, sublingual tablets, dissolution rate, bioavailability

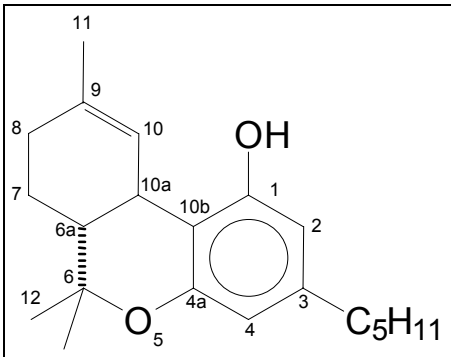
6.1. Summary

The aim of this study was to develop a dry powder formulation that stabilises the chemically labile lipophilic Δ^9-tetrahydrocannabinol (THC), that rapidly dissolves in water in order to increase the bioavailability and that opens new routes of administration. It was investigated whether these aims can be achieved with solid dispersions consisting of a matrix of inulin, an oligo-fructose, in which THC is incorporated. These solid dispersions were prepared by lyophilization of a solution of THC and inulin in a mixture of water and tertiary butyl alcohol (TBA). Both 4%w/w and 8%w/w of THC could be incorporated in a glassy matrix of inulin. In the solid dispersions only 0.4-0.5%w/w of residual TBA was present after storage at 20°C/45%RH for 7 days. Unprotected THC was completely degraded after 40 days of exposure to 20°C and 45% relative humidity. However, solid dispersions exposed to the same conditions still contained about 80% non-degraded THC after 300 days. Dissolution experiments with tablets compressed from inulin glass dispersion material showed that THC and inulin dissolved at the same rate. Tablets weighing 125 mg and containing 2 mg THC were prepared from a mixture of THC containing solid dispersion, polyvinylpolypyrrolidone (PVPP) and mannitol. Dissolution tests revealed that from these tablets 80% of the THC was dissolved within 3 minutes, which makes them promising for sublingual administration. It was concluded that THC can be strongly stabilized by incorporating it in a matrix of inulin. The aqueous dissolution rate was high which may improve bioavailability.

6.2. Introduction

Δ^9-tetrahydrocannabinol (THC) is the major pharmacologically active constituent of Cannabis sativa. It can be used as a therapeutic agent for the treatment of a large variety of diseases. Currently, the only registered indications to use THC is to relieve nausea and vomiting as a consequence of chemotherapy and to enhance appetite, particularly in AIDS patients [192]. However, also analgesic, hypotensive, anti-inflammatorial, anxiolytic and spasmolytic effects are suggested [192-194]. Furthermore, THC reduces intraocular pressure and causes broncho-dilatation [195]. The increasing interest in THC indicates a strong potential of its clinical use.
The promising pharmacological profile of THC urges the need for a suitable dosage form. However, several problems are encountered during development of a formulation for THC. THC is an oily and sticky resin that is highly viscous at ambient temperatures, which makes it almost impossible to process. Furthermore, THC is not a stable molecule. Various degradation pathways have been described by Garrett and co-workers [196]. The migration of the double bond to yield Δ8-THC and hydrolysis of the ether-linkage to yield cannabidiol are both hydrogen-ion catalysed reactions. Therefore, degradation of THC is very fast in

acidic solutions. In presence of air THC is oxidised to cannabinol [197, 198]. Degradation due to visible light is also reported [199]. The molecular structure with the dibenzopyran numbering and other relevant properties of THC are presented in figure 1.



formula	$C_{21}H_{30}O_2$
molar mass	314.47 g/mole
pKa'	10.6 (a)
logP (water pH7/octanol)	3.78 (b)
solubility in water 23 °C	2.8 mg/l (a)
solubility in 0.15 M NaCl	0.77 mg/l (a)
melting point	not detected (c)
glass transition	9.3 ºC (c)

Figure 1: Structure of (-)-Δ^9-tetrahydrocannabinol and its physico-chemical properties. (a):[200], (b): http://www.marinol.com, (c): this study

Currently, no formulation of THC is available in Europe. However, promising clinical results led to the legalization of the production and distribution of medicinal cannabis in some European countries. Attempts are being made to breed plants with high and constant levels of THC. Patients drink cannabis tea with butter in it to increase the solubility of THC. In this floating layer of melted butter all the lipophilic THC will be present which results in a very inhomogeneous dosage form. During smoking, severe degradation at extremely high temperatures, results in a bioavailability of only 15-20% [23, 153]. These rather primitive ways of extraction result in variable amounts of the active compounds released from the glands of Cannabis Sativa, causing substantial variations in the amount of administered cannabinoids. Obviously, there is a strong need for a dosage form with a constant THC content to ensure predictable delivery of THC. A formulation with a constant THC content is the soft gelatin capsule for oral administration marketed in the USA as Marinol®. The capsule is filled with sesame oil in which 2.5, 5 or 10 mg of THC is dissolved. The disadvantage is that in this formulation THC has a limited stability. As a consequence, it has to be stored at low temperatures (4°C). Moreover, due to high first pass metabolism and poor solubility, the bioavailability of THC upon oral administration is about 6% and the maximum effect is produced after 1-3 hours [23].

The aim of this study was to develop a chemically and physically stable dry powder containing THC. A stable dry powder formulation offers the possibility to develop other dosage forms e.g. tablets for oral or sublingual administration and dry powder formulations for pulmonary delivery. A second aim was to obtain a fast dissolution of THC. Solid dispersions can be used to achieve both. Solid dispersions consist of a carrier in which a compound is dispersed as small particles. When the compound is molecularly dispersed, also the term solid solutions or

amorphous glass solution is used [83]. It is known that the carrier in solid dispersions can stabilise the incorporated compound by vitrification and immobilization [17, 58, 113]. Solid dispersions are also used to accelerate dissolution of lipophilic compounds in the aqueous environment of the gastro-intestinal tract and thereby improving their oral bioavailability [6, 83, 145]. The accelerated dissolution is attributed to the large surface area, the amorphous state and improved wetting of the drug, causing carrier-controlled dissolution [32, 116].
It was previously shown that inulin stabilizes a labile protein, alkaline phosphatase, during drying and storage [151] and that lipophilic compounds could be incorporated in inulin glasses [175]. In the present study inulin is evaluated as a stabilizing carrier for THC. The effect of storage conditions and drug to carrier ratio on the stabilization is discussed. Furthermore, in vitro dissolution tests were performed to study the expected inulin controlled dissolution rate of THC and to investigate if a tablet can be formulated which rapidly releases THC.

6.3. Materials

Inulin, type TEX!803, having a degree of polymerization of 23, was kindly provided by Sensus, Roosendaal, The Netherlands. Δ^9-tetrahydrocannabinol was a generous gift of Unimed Pharmaceuticals Inc., Marietta, United States. The following materials were obtained from commercial suppliers: methanol, ethanol, n-propanol, tertiary butyl alcohol (TBA), Polyoxyethylene 20 sorbitan monooleate (Tween80®), citric acid, disodiumhydrogenphosphate, sodiumdihydrogenphosphate, CHES, and Anthrone reagent. Poly(vinyl-polypyrollidone) (PVPP) was obtained from GAF Corporation, New York, USA. Mannitol (Pearlitol® SD200 batch: E134M) was obtained from Roquette, Lestrem, France and magnesium stearate, from Janssen Chimica, Geel, Belgium. The water used was demineralised in all cases.

6.4. Methods

6.4.1. Solid dispersions prepared by spray drying

For spray drying THC was dissolved in either ethanol, n-propanol or TBA. Inulin was dissolved in water (160 mg/ml). The THC solution (10 mg/ml) was mixed with the aqueous inulin solution in a 4/6 volume ratio. In this mixture the THC concentration was 4 mg/ml, the inulin concentration was 96 mg/ml to eventually yield a product with 4%w/w THC in inulin. These solutions were physically unstable but no clouding appeared within 10 to 30 minutes, being the time necessary to spray the solution. Spray drying was performed using a Büchi 190 mini spray dryer (Büchi, Flawil, Switserland). Typical operating conditions were according to the following settings: nitrogen-gas inlet temperature: 148°C which gave an outlet temperature of 87°C, drying air flow 525 l_n/h, aspirator flow setting:

20, and pump control setting: 6. After spray drying, the formed powder was collected in a 50 ml bottle and flushed with nitrogen for about 15 minutes. The product was stored at -18 °C.

6.4.2. Solid dispersions prepared by freeze drying

For freeze drying THC was dissolved in tertiary butyl alcohol (TBA). TBA was selected because it has a high melting point (25°C). Moreover, TBA has a high vapour pressure (5.49 kPa) thereby accelerating the freeze drying process [132]. To produce a solid dispersion with 4%w/w THC, 1.20 ml of a 160 mg/ml inulin in water solution was added to 0.80 ml of a 10 mg/ml THC in TBA solution and mixed in a 20 ml vial. Similar to the solutions used for spray drying, this mixture also became cloudy after a certain lag time. At a volume ratio TBA/water of 4/6 clouding appeared after 10 minutes. Therefore, the vial was immersed in liquid nitrogen to freeze the solution immediately after mixing. Solid dispersions with 8%w/w THC were obtained by decreasing the inulin concentration. After that, the vials were freeze dried using a Christ model Alpha 2-4 lyophilizer, Salm and Kipp, Breukelen, The Netherlands. The frozen solutions were lyophilized (condensor temperature -53°C) at a shelf temperature of -35°C and a pressure of 0.220 mbar for one day. Subsequently, the shelf temperature was gradually raised to 20°C while the pressure was decreased to 0.05 mbar. These conditions were maintained for another day. After removing the samples from the freeze drier, they were stored over silicagel in a vacuum desiccator at room temperature for at least 1 day.

6.4.3. Differential Scanning Calorimetry

The thermal behaviour of THC was determined by modulated differential scanning calorimetry (MDSC) on a differential scanning calorimeter (DSC2920, TA Instruments, Gent, Belgium). A modulation amplitude of ±0.318°C every 60 sec and a heating rate of 2°C/min was used. Calibration was performed with indium at the same scanning rate. Standard aluminium sample pans were used. During measurement, the sample cell was purged with nitrogen at a flow rate of 35 ml/min. A drop of pure THC was put in the sample pan. Before analysing the sample pan was heated to 50°C. In this way the drop was able to spread over the entire bottom of the sample pan, thereby increasing the surface available for heat transfer during the second scan. In the second scan, the sample was cooled to -40°C and scanned up to 350°C.

A physical mixture of inulin and THC was obtained by weighing about 10 mg inulin in a sample pan and adding about 10 to 20 µl of a 50 mg/ml solution of THC in methanol. In this way physical mixtures were prepared containing 4%w/w and 8%w/w THC. The sample pan was heated to 60°C to allow for methanol evaporation. After cooling to -20ºC an MDSC scan was performed from -20°C to 200°C. Pure inulin and solid dispersions were scanned from -20°C to 180°C. The glass transition temperature (T_g) was defined as the inflection point of the change in specific heat in the reversing signal.

6.4.4. Investigation of effect of pH.

To test the effect of pH on stabilization of THC, different solutions were freeze dried. THC was dissolved in TBA, but inulin was dissolved in a 15.9 mM citric acid/ 8.22 mM disodiumhydrogenphospate buffer (pH 3), in demineralised water (pH 6), in a 22.0 mM CHES buffer (pH 9) or in a 44.4 mM disodiumhydrogen-phospate / 5.0 mM sodiumdihydogenphosphate buffer (pH 7.4). Freeze drying was performed according to the procedure described above. In all cases the solid dispersions contained 4%w/w THC. After 7 weeks of storage at 20°C/45%RH, 47°C/12%RH and 60ºC/8%RH the amount of non-degraded THC was determined.

6.4.5. Unformulated tablets

After preconditioning at 20°C and 45%RH, solid dispersions containing 4%w/w THC were compacted to flat 9 mm tablets of 200 mg on a hydraulic press (ESH compaction apparatus, Hydro Mooi, Appingedam, The Netherlands) at 1.0 kN. A compaction pressure of 1.0 kN was used to obtain a tablet with low friability and sufficient crushing strength (data not shown). The maximum force was reached after 2.5 seconds and was maintained for 0.1 second. After compaction the tablets were weighed and subsequently subjected to dissolution experiments.

6.4.6. Formulated tablets

Freeze dried solid dispersion material containing 8%w/w THC was pre-compacted at 5.1 MPa in a 50mm die. The pre-compacted material was broken on a Frewitt sieve (Erweka AR40, Apparatebau GmbH, Heusenstamm, Germany) with a mesh size of 0.8 mm to yield a free flowing powder. Flat 9mm tablets weighing 125 mg consisted of 25 mg solid dispersion (containing 2 mg THC), 12.5 mg PVPP, 0.625 mg magnesium stearate and 86.875 mg mannitol. Tablets were prepared with the hydraulic press at 10 kN. 10 kN compaction pressure was necessary to obtain a tablet with a low friability and sufficient crushing strength (data not shown).

6.4.7. Determination of THC content

Samples were analysed by means of HPLC using the following procedure. Methanol was added to samples. After 7 days of extraction, the sample was centrifuged and the supernatant was diluted with methanol. Validation experiments revealed that extraction was complete within 2 days for non-compressed material, but at least 4-7 days were necessary for tablets due to their lower porosities. In control experiments, no degradation was observed for at least 28 days in a 0.8 mg/ml solution of THC in methanol stored in daylight or in the dark. An ISCO model 2350 system equipped with a Photodiode Array UV-VIS Detector (Shimadzu SPD-M6A model) and a Chrompack Nucleosil 100 C18 column (4.6x250 mm) was used. Samples (20 µl) were injected with a Kontron Instruments HPLC 360 Autosampler and eluted with a mixture of methanol/water = 86/14 (v/v). The flow rate was 1.5 ml/min. The absorbance was measured at 214 nm. The collected data were analysed using SPD-MXA software. In a chromatogram of

untreated THC, a large peak was observed at a retention time of 7.5 min. In a chromatogram of THC which was intentionally partially degraded, the peak at a retention time of 7.5 min decreased in size while at shorter retention times new peaks appeared. Therefore, it was concluded that the peak at a retention time of 7.5 min can be ascribed to Δ^9-THC, while the other peaks can be ascribed to degradation products. The content of (non-degraded) THC in processed samples was calculated from the area under the peak at an elution time of 7.5 min. A calibration curve was established using solutions of THC in methanol of known concentrations ranging from 0-122 µg/ml. In every series of HPLC-runs some calibration samples were included. The solutions used for this purpose showed no significant degradation during a period of 4 weeks at 4°C. Measurements were performed at least in duplicate.

6.4.8. Stability studies

To investigate the degradation of pure THC, 70 µl of solution of THC in methanol containing 2.52 mg THC was put in 20 ml glass vials. They were left overnight under a flow of dry nitrogen to allow for methanol evaporation. The resulting thin layers of THC spread over the bottom of the vials (4.5 cm^2). The vials were stored at different conditions. A physical mixture was prepared in the same procedure except that inulin was added to the vials first, after which a THC solution was added drop wise over the inulin powder to obtain a mixture containing 4%w/w THC. Solid dispersions prepared from spray drying were weighed in vials and stored. Freeze dried samples were stored in the vials in which they were freeze dried. Samples were stored in climate chambers of 20°C/45%RH, 47°C/12%RH and 60ºC/8%RH. Samples were taken at different time intervals at least in duplicate.

6.4.9. Dissolution experiments

Dissolution was performed using a USP dissolution apparatus II (Rowa Techniek B.V., Leiderdorp, The Netherlands) at 37°C in 1000 ml under constant stirring with 100 rpm. Experiments were performed in triplicate. A dissolution medium of 1%w/v Tween80® in water was used. It was assumed that sink conditions were met. Samples were taken from the dissolution beakers to determine the THC concentration and the inulin concentration. The THC concentration in the aqueous Tween80® solutions could be determined by means of the HPLC method described above. Inulin concentrations were determined with the Anthrone assay [173]. Samples of 0.25 ml were diluted with 0.75 ml water and mixed with 2.00 ml 0.1%w/v Anthrone reagent in sulfuric acid. Due to the enthalpy of mixing, the sample was heated to its boiling point. The boiling mixture was then cooled to room temperature. After 45 minutes the sample was vortexed and 200 µl of sample was analysed spectrophotometrically at 630 nm in a 96-wells plate using a Benchmark microplate reader (Bio-Rad, Hercules, USA). A calibration curve of inulin in 0.25%w/vTween80® (0-200 mg/l) was established.

6.4.10. Determination of residual TBA

The amount of residual TBA in freeze dried samples was determined by means of Gas Chromatography (GC). Samples were weighed in 10 ml GC vials (glass vials with crimpcap with silicon/teflon septum 20mm, Chromacol Herts, United States). After dispersion in 2 ml demineralised water, the vial was centrifuged for 5 minutes at 1600 rpm and 60°C to increase sensitivity. Headspace gas chromatography was used to determine the concentration of TBA in 200 µl of the vapour. The injection temperature was 250°C. A DB wax column, 0.53 mm and 30 m with a film thickness of 1 µm was used at 50°C. A flame ionization detector (Carlo Erba Instruments GC8000 series) operating at 275°C yielded quantitative data. Control experiments showed that the peak areas were not affected by presence of sugar nor drug. For calibration pure water/TBA mixtures were used in all experiments. The amounts of residual TBA in the solid dispersions were tested immediately after freeze drying and after freeze drying followed by 7 days of exposure to 20°C and 45%RH.

6.5. Results and Discussion

6.5.1. Differential Scanning Calorimetry

DSC measurements revealed a T_g of pure THC of 9°C (see figure 2). From a thermodynamic point of view, it is expected that at temperatures just above the T_g, crystallization is likely to occur. Crystallization will be accompanied with an exothermic peak in the thermogram. However, no such peak was observed. Apparently, no crystallization occurred. This is in agreement with the fact that during storage of pure THC in our laboratory at room temperature no crystallization of THC was observed. Indeed, it has been reported before that THC resists crystallization [104]. As a consequence, at ambient temperature, THC remains in the rubbery or liquid state. Furthermore an endothermic peak with an onset at 200°C is found which could be ascribed to evaporation.

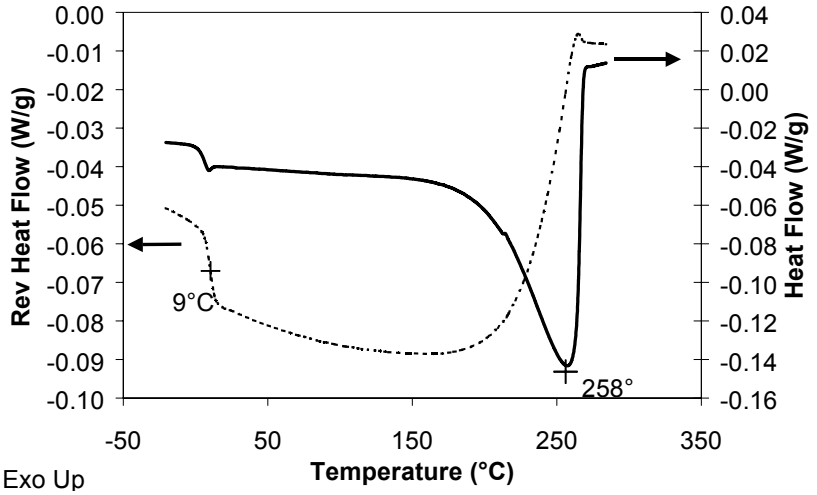


Figure 2: MDSC scan of pure THC (dashed line: reversing heatflow, solid line: total heatflow).

After lyophilization, inulin showed a glass transition at 155°C as determined by MDSC. In some of the thermograms of a physical mixture of 8%w/w THC and 92%w/w inulin, a small change in specific heat resembling a T_g was observed at 9°C. In physical mixtures containing 4%w/w THC no glass transition of THC was seen. Apparently, the amount of THC is too low to give a thermal event to be detected.

In all thermograms of the products prepared in this study one T_g was seen at about 155°C. Apparently, the T_g of the carrier inulin is not decreased by THC. A T_g reduction of a carrier due to incorporated molecules is described for example by the Gordon-Taylor equation [100]. The absence of a T_g reduction, implies that THC was not molecularly incorporated. However, if THC was not molecularly incorporated but present as small amorphous particles, two T_g's should have been observed. Because no T_g of THC is observed, no certain statements could be made about the mode of incorporation of THC.

6.5.2. Stability of unprotected THC

When pure THC was exposed to air its colour rapidly changed from yellow to purple and subsequently to brown. These colour changes indicate degradation of the material [197]. Therefore, during handling air contact was avoided as much as possible. To prepare samples with pure THC and physical mixtures solutions of THC in methanol were used. After evaporation of methanol under a flow of nitrogen, samples were slightly purple. Apparently, traces of oxygen were still present during evaporation. At the start of the study to evaluate the stability of unprotected THC, about 93% of the THC could be recovered in the pure samples and about 95% in the physical mixtures, indicating THC degradation during sample preparation. All samples became intense purple after a few hours and turned brown

after a few days. In the stability studies, the amount of non-degraded THC was related to these initial values.

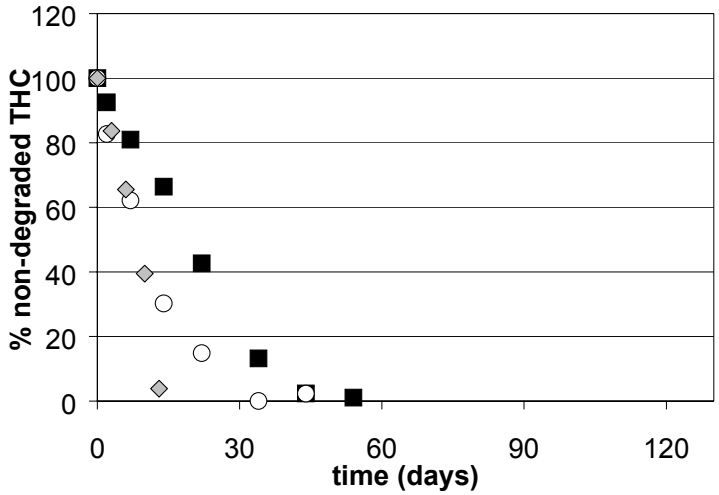


Figure 3: Degradation of pure THC
(Key: ■ 20°C/45%RH, ○ 47°/12%RH, ◆ 60°C/8%RH)

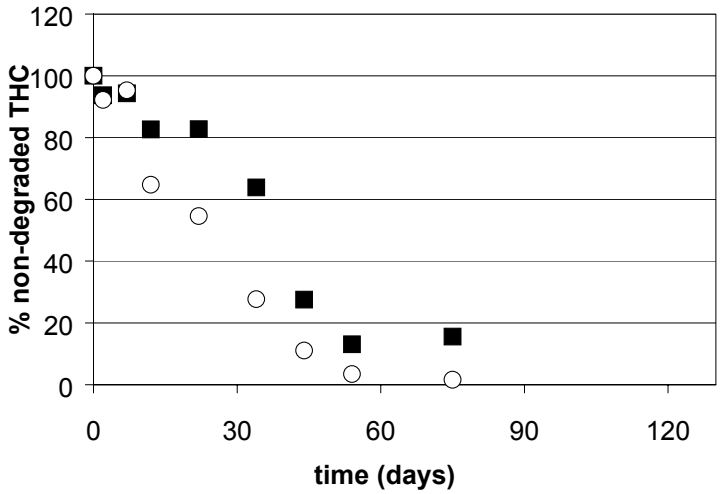


Figure 4: Degradation of THC in a physical mixture containing 96%w/w inulin
(Key: ■ 20°C/45%RH, ○ 47°/12%RH)

As can be seen in figures 3 and 4, degradation of unprotected THC is very fast and is accelerated at elevated temperatures. Degradation in the physical mixture is a little bit slower. This can be due to partial incorporation of THC in inulin during preparation of physical mixtures. During absorption of the methanolic solution into

inulin, a part of the dissolved THC molecules are dragged along with the methanol into the matrix of inulin, facilitated by the softening of inulin.
In our laboratory, the THC supply was stored under nitrogen atmosphere but was exposed to daylight. No changes in THC content were observed within at least a year. Therefore, the reported light induced degradation of THC [199] was not observed in this study. But it is clear that unprotected THC is very unstable when exposed to air.

6.5.3. Stability of THC in spray dried samples

Preliminary experiments showed that the powder turned from white to purple during spray drying, indicating degradation of THC. Spray drying in a nitrogen atmosphere postponed the change in colour to the moment of sample collection, during which the powder came in contact with air. Therefore, spray drying in nitrogen was continued in all further experiments. When spray drying from TBA-water mixtures all THC could be recovered immediately after spray drying. Two different batches were prepared. Their stability is shown in figure 5.

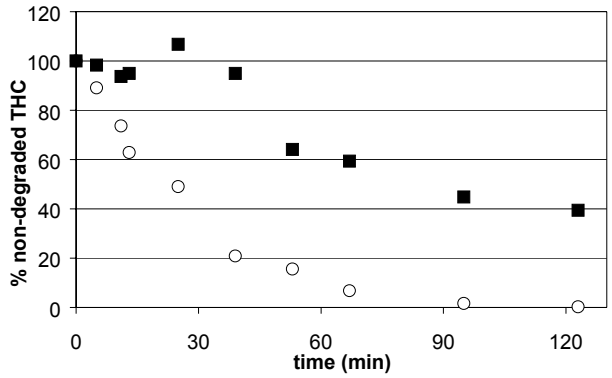


Figure 5: Degradation of THC after spray drying with inulin in water-TBA (Key: ■ 20°C/45%RH, ○ 47°/12%RH n=3 S.D. ≤ 4.2%)

Although THC in the spray dried samples degraded significantly slower than unprotected THC, there is still room for improvement. Apparently, partial phase separation of inulin and THC occurs during evaporation of the solvents from droplets during the drying phase. TBA being more volatile, will evaporate faster than water. The premature supersaturation of THC in the evaporating droplet will result in phase separation while inulin is still dissolved. This prohibits proper inclusion in the inulin matrix. Spray-drying was also performed using ethanol-water and n-propanol-water as solvent mixtures. Stability of THC in those batches was even somewhat worse than when TBA-water mixtures were used (data not shown). It can be concluded that spray drying does improve THC stability. However, under these conditions it did not result in a product with a desired stability.

6.5.4. Stability of THC in freeze dried samples

After freeze drying, 100% of the THC could be recovered in the inulin matrix. Furthermore, the stability of THC in freeze dried samples was strongly improved as can be seen in figures 6 and 7. The reproducibility is appreciable, considering the fact that these figures present data of 10 different batches prepared fully independently. After 300 days of exposure to 20°C and 45%RH, only about 20% of the incorporated THC was degraded, while this takes only less than 10 days for unprotected THC (see figure 3). Clearly, THC is incorporated in the inulin glass in such a way that it is highly stabilised. Apparently, freeze drying using TBA and water as solvents is a far more better way to incorporate and stabilise THC in inulin glasses than spray drying. It can be concluded that with the freeze drying method solid dispersions are obtained in which THC is protected from its environment by inulin. The samples did not collapse at any of the conditions used in this study. This indicates that the carrier inulin maintained in the glassy state. THC degraded faster at 47°C/12%RH and at 60°C/8%RH THC degradation was fastest. Clearly, temperature has a pronounced effect in the stability of THC.

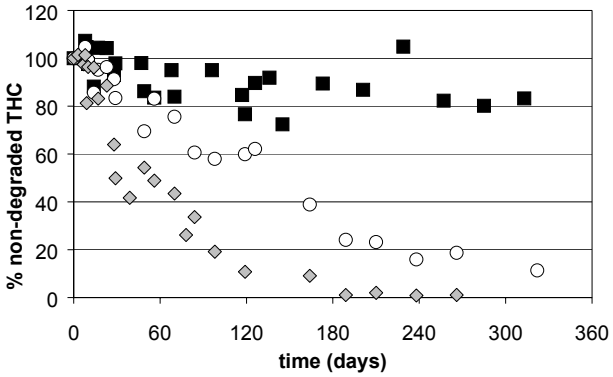


Figure 6: Stabilization of THC by inulin in freeze dried cakes containing 4%w/w THC (n=2-3 S.D. ≤11% Key: ■ 20°C/45%RH, ○ 47°/12%RH, ◆ 60°C/8%RH)

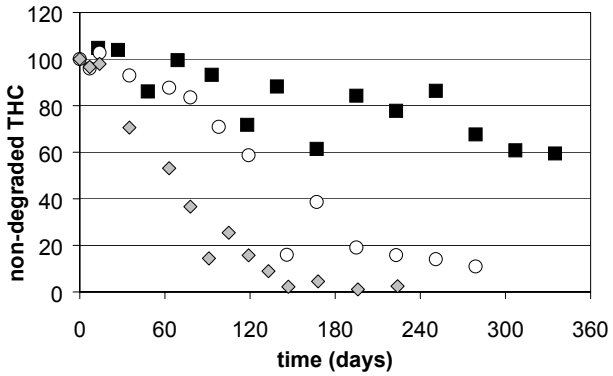


Figure 7: Stabilization of THC by inulin in freeze dried cakes containing 8%w/w THC (n=2-3 S.D. ≤15% Key: ■ 20°C/45%RH, ○ 47°/12%RH, ◆ 60°C/8%RH)

6.5.5. Effect of pH

The stability of THC in solid dispersions freeze dried from aqueous buffer/TBA mixtures is depicted in figure 8. Samples exposed to 47°C/12%RH or 60ºC/8%RH, were all stabilised to the same extent, irrespective of pH. However, in samples exposed to increased humidity (20°C/45%RH), stabilization of THC was largely affected by the pH of the solution from which the solid dispersion was prepared: THC remained unaffected in solid dispersions prepared from solutions of pH 6 (demineralised water) or pH 9, but degraded substantially if the solid dispersion was prepared by freeze drying a solution at pH 3. Apparently, the uptake of a certain minimum amount of water is necessary to facilitate the damaging action of a low pH. This behaviour corresponds with the results of Garrett and co-workers [196], who found that in acidic solutions THC degraded faster. From these experiments, it can be concluded that pH can be an important factor in the stabilization of THC in inulin glass dispersions.

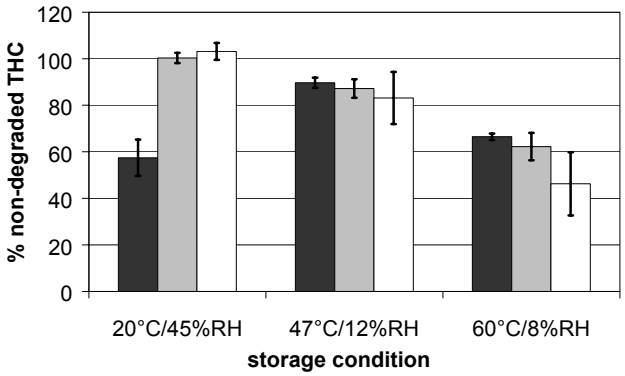


Figure 8: Amount of THC in inulin glasses after storage for 7 weeks (4%w/w THC) prepared by freeze drying solutions with different pH's (n=3 ± S.D., Key: ■ pH3, ■ demi, □ pH 9)

6.5.6. Dissolution of tablets

Tablets were prepared from pure lyophilised solid dispersion material. No disintegrants or other additives were used. The tablets contained 4%w/w THC incorporated in inulin. It should be mentioned that all tablets had a sufficient tensile strength and low friability (data not shown). The excellent binding capacities of amorphous inulin has been described before [201].

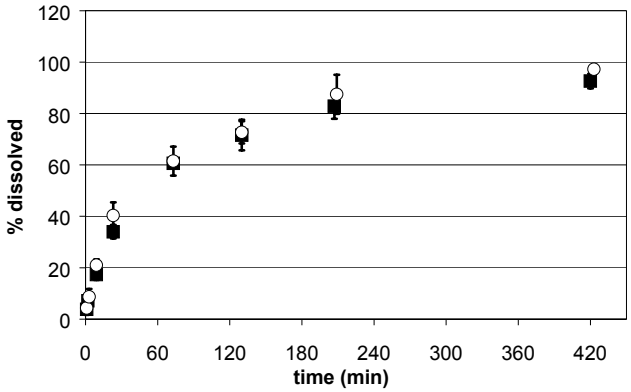


Figure 9: Dissolution of tablets consisting of solid dispersion containing 4%w/w THC (n=5, mean ± S.D. Key: ■: THC, ○: inulin)

Both THC and inulin concentrations were measured during dissolution of the tablets. From figure 9 it can be seen that the dissolution of inulin coincides completely with the dissolution THC. The dissolution rate of the lipophilic THC is fully governed by dissolution of the carrier inulin, as was expected with solid dispersions [32, 83]. The carrier controlled dissolution, illustrated in figure 9, offers the possibility to control the dissolution rate of THC by using appropriate tablet formulations. An example of the dissolution of a formulated tablet is shown in figure 10. The tablet (125 mg, containing 2 mg THC) dissolved rapidly: 80% of the THC was dissolved within about 3 minutes. Clearly, this experiment shows that aqueous dissolution of the lipophilic THC from this tablet is very fast, making it promising for sublingual administration. It can be expected that the bioavailability of THC is increased by using such a tablet because sublingual administration circumvents first pass metabolism and secondly because of the fast dissolution of THC. Therefore, the THC content was lower than in the Marinol® capsule, which contains 2.5, 5 or 10 mg THC.

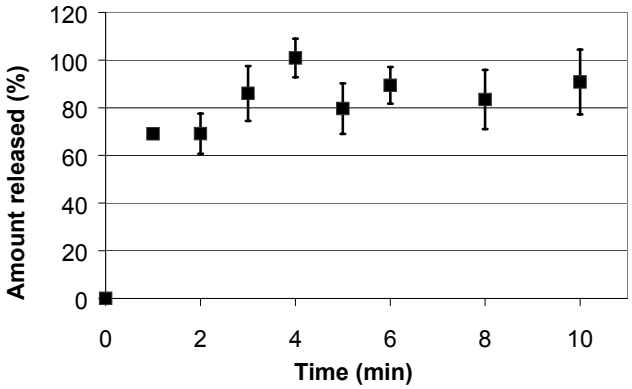


Figure 10: Dissolution of THC from sublingual tablets (n=3, mean ± S.D)

6.5.7. Residual TBA contents

Based on toxicity data, TBA is likely to fall into the category of class III solvents [132]. Nevertheless, the residual amount of TBA was determined immediately after freeze drying and after freeze drying with subsequent storage for 7 days at 20°C/45%RH. Samples without and with 4%, 8%w/w THC were analysed. From table 1 it can be clearly seen that the post-treatment strongly reduced the amount of residual TBA. Furthermore, the presence of THC causes a linear increase in retention both immediately after freeze drying and after subsequent storage for 7 days at 20°C/45%RH. Apparently, TBA is retained partially by the lipophilic THC. Because the maximally allowed dose for TBA is 50 mg/day for class III solvents, it can be calculated that 64 mg of THC can be administered each day for a freshly prepared 4%w/w solid dispersion. Even more THC can be administered if the solid dispersions are stored for 7 days at 20°C/45%RH or if they contain 8%w/w THC. The amount of THC that can be administered is much higher than the highest dose currently used in the clinic (10 mg in Marinol® capsule). Therefore, it can be concluded that the residual amount of TBA is not restrictive for clinical application of THC containing solid dispersions.

Table 1: TBA content in solid dispersions (n=2-4 ± standard deviation)

	TBA content (%w/w)	
	0 days	7 days at 45%RH/20°C
no THC	2.43 ± 0.17	0.26 ± 0.00
4%w/w THC	3.08 ± 0.34	0.38 ± 0.02
8%w/w THC	3.37 ± 0.11	0.50 ± 0.00

6.6. Conclusion

In this study, it is shown that lyophilising a solution of the oligo-saccharide inulin and the THC in a mixture of water and TBA, results in the formation of a solid dispersion. Furthermore the chemically labile THC can be stabilised by the incorporation in the glassy inulin matrix. The dry powder obtained in this way is very promising for the development of more convenient and reliable dosage forms. It was shown that tablets can be formulated from which THC is dissolved very fast. The dissolution rate limited oral bioavailability of THC is expected to be increased.

6.7. Acknowledgements

The authors would like to thank Solvay Pharmaceuticals (Weesp, The Netherlands) for financial support. Furthermore we would like to thank Rein Bos from the department of Pharmaceutical Biology (RuG, The Netherlands) for helping us setting up the HPLC assay, Esther Geelen for performing part of the dissolution experiments and the people at the pharmacy of the Groningen University Hospital for performing GC measurements for determination of TBA contents.